CLINICAL AND HORMONAL PROFILE

OF

HYPOGONADISM

Dissertation submitted in partial fulfillment of requirements for

M.D. DEGREE IN GENERAL MEDICINE

BRANCH I

Of

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY,

CHENNAI, INDIA.

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MARCH 2009

DECLARATION

I solemnly declare that this dissertation entitled "**CLINICAL AND HORMONAL PROFILE OF HYPOGONADISM**" was done by me at Madras Medical College and Government General Hospital, during 2006-2009 under the guidance and supervision of **Prof. K. RAGHAVAN, M.D.** This dissertation is submitted to the Tamil Nadu Dr.M.G.R. Medical University towards the partial fulfillment of requirements for the award of M.D. Degree in General Medicine (Branch-I).

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ACKNOWLEDEGEMENT

At the outset I thank **Prof. T.P.KALANITI, M.D.,** Dean Madras Medical College, for having permitted me to use the hospital resources for the study.

I am immensely grateful to **Prof. C. RAJENDIRAN, M.D.,** Director and Professor, Institute of Internal Medicine, for his suggestions and encouragement.

I express my deep gratitude to **Prof. K. RAGHAVAN, M.D.,** former Director and Professor, Institute of Internal Medicine, for his inspiration, advice, comments and guidance to complete this work.

I am ever grateful to **Prof. A. RADHAKRISHNAN, M.D.,** Professor, Institute of Internal Medicine, who has extended all his support.

I express my sincere thanks to Assistant Professors of Institute of Internal Medicine **DR. HARIDOSS SRIPRIYA VASUDEVAN, M.D.,** and **DR. USHA LAKSHMI, M.D.,** and **DR. SARAVANA BABU, M.D.,** for their guidance and help.

Lastly, I express my gratitude and sincere thanks to the patients who were kind and co-operative during the course of the study.

CERTIFICATE

This is to certify that the dissertation entitled "**CLINICAL AND HORMONAL PROFILE OF HYPOGONADISM**" is a bonafide work done by **Dr. JEGAN NIWAS. K.,** at Madras Medical College, Chennai in partial fulfillment of the university rules and regulations for award of M.D., Degree in General Medicine (Branch-I) under my guidance and supervision during the academic year 2006-2009.

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CONTENTS

INTRODUCTION

Hypogonadism is an important reason for boys and girls attending the endocrinology clinic.

Delayed Puberty or decreased development of secondary sexual characters has to be evaluated, if puberty is not attained by age 14 years in boys and age 13 years in girls, an age that is 2-2.5 standard deviations above the mean for healthy children.

Delayed puberty is more common in boys than girls.

There are four main categories of delayed puberty:

1. Constitutional delay of growth and puberty (60% of cases),
2. Functional hypogonadotropic hypogonadism caused by

Systemic illness or malnutrition (20% of cases),

3. Hypogonadotropic hypogonadism caused by genetic or acquired defects in the hypothalamic-pituitary regions (10% of cases),

4. Hypergonadotropic hypogonadism secondary to primary gonadal failure (15% of cases).

Functional hypogonodotropic hypogonadism is more common in girls than in boys, due to their increased susceptibility to adverse effects of energy imbalance resulting from dieting, exercise and or eating disorders.

In this study, an attempt is made to identify and appropriately classify patients presenting with hypogonadism. Optimal therapeutic interventions could help in physical development and overcome emotional trauma.

AIMS AND OBJECTIVES

1. To evaluate the aetiology of hypogonadism in individuals who present with reduced secondary sexual characters or delayed puberty.

2. To find out the type of hypogonadism as either hypogonadotropic or hypergonadotropic and to treat them accordingly.

REVIEW OF LITERATURE

Hypogonadism is broadly classified into hypogonadotropic hypogonadism and hypergonadotropic hypogonadism. Hypogonadism can be congenital or acquired.

Hypogonadotropic hypogonadism implies pituitary hormonal deficiency or hypothalamic hormone deficiency, whereas hypergonadotropic hypogonadism

implies primary gonadal failure and subsequent increase in the level of pituitary hormones.

FOLLOWING ARE THE CAUSES FOR DELAYED PUBERTY OR HYPOGONADISM IN BOYS [16, 18]

A. Constitutional delay of growth and puberty.

B. Systemic disorders- chronic disease, malnutrition and anorexia nervosa

C. Functional disorders due to excessive exercise, dieting and usage of Anabolic Steroids.

D. Structural causes-

Tumors- craniopharyngioma, germinoma, gliomas, meningiomas

Infiltrative disorders- like Sarcoidosis, Hemochromatosis

and Histiocytosis X

E. Head Trauma, Radiotherapy and surgery

A.

B. Hypothalamic-hypophyseal causes of pubertal failure (low gonadotropins)

1. Congenital disorders

    a. Hypothalamic syndromes like Prader-Willi syndrome.

    b. Idiopathic hypogonadotropic hypogonadism-congenital or adult onset

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    d. Kallmann syndrome

    e. GnRH receptor mutations

    f. Adrenal hypoplasia congenita

    g. PROP1 mutations

    h. Other mutations affecting pituitary development/function

2. Acquired disorders.

    a. Pituitary tumors like pituitary adenoma.

    b. Hyperprolactinemia

Hypergonadotropic hypogonadism in males

Gonadal causes of pubertal failure (Elevated Gonadotropins)

1. Klinefelter syndrome
2. Bilateral undescended testes or anorchia (vanishing testis syndrome

   Or testicular regression syndrome)[14]

3. Orchitis
4. Chemotherapy or radiotherapy
5. Androgen insensitivity
6. Inactivating mutations of

   LH beta subunit

   FSH beta subunit

   LH receptor

   FSH receptor

7. Sertoli cell only syndrome.

8. LH resistance.

9. Testicular biosynthetic defects.

Differential diagnosis of delayed puberty in girls is:

Hypergonadotropic hypogonadism

- **Ovarian**

  1. Turner syndrome

  2. Gonadal dysgenesis with mosaic karyotype

  3.

  4. Pure Gonadal dysgenesis (Swyer syndrome)

  5. Chemotherapy/radiation therapy

  6. Galactosemia

  7. Autoimmune oophoritis

  8. Congenital lipoid hyperplasia

- Steroidogenic enzyme abnormalities

  1. 17 alpha-hydroxylase abnormalities

2. Aromatase deficiency

- Gonadotropin/receptor mutations

FSH beta, LHR, FSHR

- Androgen resistance syndrome

Hypogonadotropic hypogonadism

GENETIC

- Hypothalamic syndromes due to mutation of

Leptin/leptin receptor

HESX1 (septooptic dysplasia)

PC1 (prohormone convertase)

- Idiopathic hypogonadotropic hypogonadism and Kallmann

  Syndrome due to mutation of genes-KAL, FGFR1, GnRHR, GPR54

- Abnormalities of pituitary development/function - PROP1

CNS TUMORS/INFILTRATIVE DISORDERS

1. Craniopharyngioma[21]

2. Astrocytoma, germinoma, glioma
3. Prolactinomas, other pituitary tumors
4. Histiocytosis X
5. Chemotherapy/radiation

FUNCTIONAL

1. Chronic diseases
2. Malnutrition
3. Excessive exercise
4. Eating disorders

Anomalies of the genital tract

- Müllerian agenesis (e.g. Mayer-Rokitansky-Kuster-Hauser syndrome) breast present with rudimentary or absent uterus
- Congenital or acquired anatomic obstruction (e.g., imperforate hymen, transverse vaginal septum, Asherman syndrome, endometrial destruction due to severe infection or surgery)

- Androgen insensitive syndrome (absent uterus with normal breast development)

Androgen Insensitivity Syndrome

Mutations in the androgen receptor cause resistance to androgen (testosterone, DHT) action causing Androgen Insensitivity Syndrome (AIS). AIS are a spectrum of disorders that affect 1 in 100,000 chromosomal males. Because the androgen receptor is X-linked, only males are affected and maternal carriers are phenotypically normal. XY individuals with complete AIS (formerly testicular feminization syndrome) have a female phenotype, normal breast development (due to aromatization of testosterone), a short vagina but no uterus (because Mullerian Inhibiting Substance production is normal), scanty pubic and axillary hair, and female psychosexual orientation. Gonadotropin levels low, normal or elevated, depending on the degree of androgen resistance and the contribution of estradiol to feedback inhibition of the hypothalamic-pituitary gonadal axis. Most patients present in childhood with inguinal herniae (containing testes) or with primary amenorrhea in adulthood. Gonadectomy is usually performed, as there is a low risk of malignancy, and estrogen supplementation is prescribed. Alternatively, the

gonads can be left in situ until breast development is complete. The use of graded dilators in adolescence is usually sufficient to dilate the vagina and permit sexual intercourse.

Partial AIS (Reifenstein syndrome) results from less severe loss of Androgen receptor mutations. Patients often present in infancy with perineoscrotal hypospadias, small undescended testes, and with gynecomastia at the time of puberty. Those individuals raised as males require hypospadias repair in childhood and breast reduction in adolescence. Supplemental testosterone rarely enhances androgenization significantly, as endogenous testosterone is already increased. More severely underandrogenized patients present with clitoral enlargement and labial fusion and may be raised as females. The surgical and psychosexual management of these patients is complex and requires active involvement of parents and the patient during the appropriate stages of development.

HYPOGONADOTROPIC HYPOGONADISM

Secondary hypogonadism results by impaired secretion of pituitary gonadotropins, luteinizing hormone and follicle stimulating hormone is characterized by low testosterone or low estradiol in the setting of low LH (Luteinizing hormone) and low FSH (follicle-stimulating hormone).

Patients with severe deficiency of have complete absence of pubertal development, sexual infantilism and in some cases, causes hypospadias and undescended testis in males. Patients with partial gonadotropin deficiency have delayed or arrested sex development.

Hypogonadotropic hypogonadism can be classified into congenital and acquired disorders. Congenital disorders most commonly involve GnRH (Gondotropin releasing hormone), which leads to gonadotropin deficiency. Acquired disorders are much more common than congenital disorders and may result from variety of sellar mass lesions or infiltrative diseases of the hypothalamus or pituitary.

CONGENITAL DISORDERS ASSOCIATED WITH GONADOTROPIN DEFICIENCY

Most cases of congenital hypogonadotropic hypogonadism are idiopathic, despite extensive endocrine testing and imaging studies of the sellar region. Among known causes, familial hypogonadotropic hypogonadism can be transmitted as an X-Linked (20%), autosomal recessive (30%) or autosomal dominant (50%) trait.

Idiopathic hypogonadotropic hypogonadism and Kallmann syndrome are characterized by an isolated defect in GnRH secretion as evidenced by [16]

1. Complete or partial absence of any GnRH-induced LH pulsations.
2. Normalization of pituitary and gonadal function in response to physiologic regimens of exogenous GnRH replacement.
3. Normal baseline and reserve testing of the remainder of the hypothalamic-pituitary axes and
4. Normal findings on radiographic imaging of the hypothalamic-pituitary region.

Kallmann syndrome is an X-linked disorder caused by mutations in the KAL1 gene, which encodes anosmin, a protein that mediates the migration of neural progenitors of the olfactory bulb and GnRH- producing neurons.

These individuals have GnRH deficiency and variable combinations of anosmia or hyposmia, renal agenesis, synkinesia, cleft lip, cleft palate, oculomotor/visuospatial defects, gut malrotations and mirror movements. In

MRI there will be absence of anomalous morphology or absent olfactory bulbs which provides us a presumptive diagnosis of Kallmann syndrome. [24] In individuals with Kallmann syndrome Gondatropin secretion and fertility can be restored by administration of pulsatile GnRH or by gonadotropin replacement. [17]

Mutations in the FGFR1 gene cause an autosomal dominant form of hypogonadotropic hypogonadism that resembles Kallmann syndrome. Prokineticin 2(PROK2) also encodes a protein involved in migration and development of olfactory and GnRH neurons. Recessive mutations in the PROK2 cause anosmia and hypogonadotropic hypogonadism. X-linked hypogonadotropic hypogonadism also occurs in adrenal hypoplasia congenita, a disorder caused by mutations in the DAX1 gene, which encodes a nuclear receptor in the adrenal gland and reproductive axis.

Adrenal hypoplasia congenital is characterized by absent development of the adult zone of adrenal cortex, leading to neonatal adrenal insufficiency. Puberty usually does not occur or is arrested, reflecting variable degrees of gonadotropin deficiency.

Mutations of steroidogenic factor 1 (SF1) less commonly cause sex reversal and hypogonadotropic reversal. GnRH receptor mutations account for approximately 40% of the autosomal recessive and 10% of sporadic cases of hypogonadotropic hypogonadism.

Recessive mutations in the G-protein-coupled receptor GPR54 cause gonadotropin deficiency without anosmia. A number of homeodomain transcription factors are involved in the development of differentiation of the specialized hormone producing cells within the pituitary gland.

Mutations in GPR54, a G protein–coupled receptor gene, cause autosomal recessive idiopathic hypogonadotropic hypogonadism in humans and mice, suggesting that this receptor is essential for normal gonadotropin-releasing hormone physiology and for puberty. [28]

Patients with mutations of PROP1 have combined pituitary hormone deficiency that includes GH, prolactin, thyroid-stimulating hormone, LH and FSH, but not ACTH. LHX3 mutations cause combined pituitary hormone deficiency in association with cervical spine rigidity. HESX1 mutations cause septooptic dysplasia and combined pituitary hormone deficiency.

There are two syndromes commonly associated with hypogonadism are Prader-Willi syndrome and Lawrence-Moon syndrome. Prader-Willi syndrome is characterized by obesity, hypotonic musculature, mental

retardation, hypogonadism, short stature and small hands and feet. Prader Willi syndrome is a genomic imprinting disorder caused by deletions of the proximal portion of the paternal chromosome 15q. Uniparental disomy of the maternal alleles or mutations of the genes/loci are involved in imprinting.

Lawrence-Moon syndrome is an autosomal recessive disorder characterized by obesity, hypogonadism, mental retardation, polydactyly and retinal pigmentosa. Recessive mutations of leptin, or its receptor, cause severe obesity and pubertal arrest, apparently because of hypothalamic GnRH deficiency.

ADULT ONSET IDIOPATHIC HYPOGONADOTROPIC HYPOGONADISM

In this group of patients, puberty occurs normally, but post pubertal, there is decrease in libido and fertility in the presence of testes that are of normal or near normal size. Biochemically these patients cannot be distinguished from subjects with congenital GnRH deficiency in that they have a pulsatile pattern of LH secretion associated with low serum testosterone levels. Recent studies have demonstrated that after a period of GnRH or hCG

administration in patients with IHH, reversal of hypogonadism is possible and those patients had sustained adult levels of testosterone even after discontinuation of hormonal therapy. [17]

VARIANT OR PARTIAL FORMS OF GNRH DEFICIENCY: FERTILE EUNUCH SYNDROME. [16]

The fertile eunuch syndrome is thought to represent an incomplete form of GnRH deficiency. In this disorder, the enfeebled endogenous GnRH secretion is sufficient to achieve the intra-testicular testosterone concentrations needed to support spermatogenesis and testicular growth but is insufficient to achieve the systemic testosterone levels necessary for full virilization. The clinical presentation of fertile eunuch is similar to that of mid pubertal boys.

The Fertile Eunuch Variant of Idiopathic Hypogonadotropic Hypogonadism: [26] Spontaneous Reversal Associated with a Homozygous Mutation in the Gonadotropin-Releasing Hormone Receptor-1 is achieved with treatment of hCG even for few (4)months . Following cessation of hCG therapy, the patient demonstrated reversal of his hypogonadotropism as evidenced by normal adult male testosterone levels and the appearance of pulsatile luteinizing hormone secretion.

TREATMENT

IHH men have an incomplete GnRH deficiency and that long term exogenous GnRH administration induces pituitary and gonadal priming, which subsequently enables them to sustain normal pituitary and gonadal function in response to their own enfeebled GnRH secretion. [25]

Human Chorionic Gonadotropin (hCG), in the absence of exogenous FSH, can complete spermiogenesis in men with partial gonadotropin deficiency. The response to hCG in men with IHH is predicted by the initial testicular volume. [23]

Although a variety of treatment regimens are used, 1500-2000 IU of hCG or recombinant human LH administered intramuscularly three times weekly is a reasonable starting dose. Testosterone levels should be measured 6-8 weeks later and 48-72 hours after the hCG or LH injection; HCG/rhLH dose should be adjusted to achieve testosterone in the mid-normal range. It may take several months for the spermatogenesis to be restored, therefore it is important to forewarn patients about the potential length and expense of the treatment and to provide conservative estimates of success rates. If testosterone levels are in the mid-normal range but the sperm concentrations are low after 6 months of therapy with hCG alone, FSH should be added.

A common practice is to start with the addition of 75 IU FSH three times each week in conjunction with hCG injections.

The two best predictors of success using gonadotropin therapy in hypogonadotropic men are testicular volume at presentation and time of onset. In general, men with testicular volumes > 8ml have better response rates than those who have testicular volumes < 4 ml. Patients who became

hypogonadotropic after puberty experience higher success rates than those who have never undergone pubertal changes. Spermatogenesis can usually be reinitiated by hCG alone, with high rates of success for men with post pubertal onset of hypogonadotropism. Prior androgen therapy does not affect subsequent response to gonadotropin therapy.

GnRH (Gonadotropin Releasing Hormone)

In patients with documented GnRH deficiency, both pubertal development and spermatogenesis can be successfully induced by pulsatile administration of low doses of GnRH. This response requires normal pituitary and testicular function. Therapy usually begins with an initial dose of 25ng/kg

per pulse administered subcutaneously every 2 hour by a portable infusion pump. Testosterone, LH and FSH levels should be monitored.

However, most patients find intermittent gonadotropin injections preferable to wearing a continuous infusion pump.

ACQUIRED HYPOGONADOTROPIC DISORDERS

Severe Illness, Malnutrition and Exercise:

These may cause reversible gonadotropin deficiency. Although gonadotropin deficiency and reproductive dysfunction are well documented in these conditions in women, men exhibit similar but less pronounced responses.

The magnitude of gonadotropin suppression correlates with the severity of illness. The pathophysiology of reproductive dysfunction is unknown but likely involves combined cytokine and glucocorticoid effects.

There is a high frequency of low testosterone levels in patients with chronic illness such as HIV infection, end stage renal disease, chronic obstructive lung disease and many types of cancer and in patients receiving glucocorticoids.

Muscle wasting is common in chronic diseases associated with hypogonadism which also leads to debility, poor quality of life and adverse outcome of disease. There is a great interest in exploring strategies that can reverse androgen deficiency or attenuate the sarcopenia associated with chronic illness. Men using opioids for cancer or noncancerous pain or because of addiction often have suppressed testosterone and LH levels, the degree of suppression is dose related. Opioids suppress GnRH secretion and alter the sensitivity to feedback inhibition by gonadal steroids.

Men who are heavy users of marijuana have decreased testosterone secretion and sperm production.

OBESITY

In men with mild to moderate obesity, Sex Hormone Binding Globulin (SHBG) levels decrease in proportions to the degree of obesity, resulting in lower total testosterone levels. However, free testosterone levels usually remain within the normal range. The decrease in SHBG levels is caused by increased circulating insulin, which inhibits SHBG production. Estradiol levels are higher in obese men compared to healthy, non obese controls, because of aromatization of testosterone to estradiol in adipose tissue. Weight loss is associated with reversal of these abnormalities including an increase in total and free testosterone levels and a decrease in estradiol levels.

HYPERPROLACTINEMIA

Elevated levels of prolactin are associated with hypogonodatropic hypogonadism. Prolactin inhibits hypothalamic GnRH secretion either directly or through modulation of tuberoinfundibular dopaminergic pathways. A prolactin secreting tumor may also destroy the surrounding gonadotropes by invasion or compression of the pituitary stalk. Treatment with dopamine agonists reverses gonadotropin deficiency.

SELLAR MASS LESIONS

Tumors in the CNS can compress the portal vessels and impede the flow of GnRH from the hypothalamus to the pituitary gland. Pituitary adenomas, craniopharyngiomas, and meningiomas are examples of slow-growing nonmetastatic tumors that are uncommon causes of hypogonadotropic hypogonadism. Anterior pituitary prolactinomas releasing prolactin hormone are the most common pituitary tumors to cause hypogonadotropic hypogonadism.

Other acquired disorders can disrupt pituitary function by destructive means, such as ischemia, infiltration, and obstruction. Head trauma, cranial aneurysms, and infiltrative processes (e.g., sarcoidosis, syphilis, tuberculomas) are examples of conditions that can disrupt pituitary function.

Pituitary adenomas that extend into the supra-sellar region can impair GnRH secretion and mildly increase prolactin usually less than 50 micro-liters because of the impaired tonic inhibition by dopaminergic pathways. These tumors should be distinguished from prolactinomas which secrete higher levels of prolactin. The presence of diabetes insipidus suggests the possibility of a craniopharyngioma, infiltrative disorder, or other hypothalamic lesions.

HEMOCHROMATOSIS

Hemochromatosis is a common inherited disorder of iron metabolism in which an inappropriate increase in intestinal iron absorption results in deposition of excessive amounts of iron in parenchymal cells with eventual tissue damage and impaired organ function.

Both pituitary and testis can be affected by excessive iron deposition. However, the pituitary is the predominant lesion in most patients with hemochromatosis and hypogonadism. The diagnosis of hemochromatosis is suggested by the association of characteristic skin discolouration, hepatic enlargement or dysfunction, diabetes mellitus, arthritis, cardiac conduction defects and hypogonadism.

PRIMARY GONADAL FAILURE

PRIMARY TESTICULAR CAUSES OF HYPOGONADISM

Common causes of primary testicular dysfunction include Klinefelter syndrome, uncorrected cryptorchidism, and cancer, chemo therapy radiation to the testis, trauma, torsion, infectious orchitis, HIV infection, anorchia syndrome and myotonic dystrophy. Primary testicular disorders may be associated with impaired spermatogenesis, decreased androgen production, or both.

CONGENITAL CAUSES:

Klinefelter Syndrome:

Klinefelter Syndrome is the most common chromosomal disorder associated with testicular dysfunction and male infertility. It occurs once in 1000 live-born males. Azoospermia is the rule in men with Klinefelter syndrome who have the 47XXY karyotype; however, men with mosaicism may have germ cells, especially at a younger age. Testicular histology shows hyalinization of seminiferous tubules and absence of spermatogenesis.

Although their function is impaired, the number of Leydig cells appears to increase. Testosterone is decreased and estradiol is increased, leading to clinical features of undervirilization and gynecomastia. Men with Klinefelter syndrome are at increased risk of breast cancer, non-Hodgkin's lymphoma and lung cancer and reduced risk of prostate cancer. Periodic mammography for breast cancer surveillance is recommended for men with Klinefelter Syndrome.

Cryptorchidism

Cryptorchidism occurs when there is incomplete descent of the testis from the abdominal cavity into the scrotum. About 30% of premature male infants have at least one cryptorchid testis at birth, but descent is usually

complete by the first few weeks of life. The incidence of cryptorchidism is <1% by 9 months of age. Crytorchidism is associated with increased risk of malignancy and infertility. Unilateral cryptorchidism, even when corrected before puberty, is associated with decreased sperm count, possibly reflecting unrecognized damage to the fully descended testis or other genetic factors. Epidemiologic, clinical and molecular evidence supports the idea that cryptorchidism, hypospadias, impaired spermatogenesis, and testicular cancer may be causally related to common genetic and environment perturbations and are components of the testicular dysgenesis syndrome.

VANISHING TESTIS SYNDROME- BILATERAL ANORCHIA

The vanishing or regressed testis is an entity well known to urologists and pediatric surgeons, affecting approximately 5% of patients with cryptorchidism.

"Vanishing testis syndrome" otherwise called as bilateral anorchia or "testicular regression syndrome" or 46 XY gonadal dysgenesis is characterized by the absence of testis in a 46XY individual with a male phenotype and is an important and a well known cause of bilateral absent testis.

Non-palpable testicles may be due to the vanishing testis syndrome, intra-abdominal position, examination obscured by obesity or scar tissue and rarely testicular agenesis. Laparoscopy is an excellent means of distinguishing these entities without the need for open abdominal exploration. [9]

The etiology is unknown; however, the familial occurrence of the disease and the association of this phenotype with 46XY gonadal dysgenesis have led to the suggestion that genetic factors, which play a role in testicular determination, may be involved. Alternatively, exploratory laparoscopy has suggested that anorchia may be caused by a prenatal testicular vascular accident associated with torsion during testicular descent. [14]

Heterozygous partial loss of function mutations in SF1 may be associated with bilateral anorchia (‘vanishing testis syndrome’) and micropenis in humans. [27]

These patients can acquire secondary sexual characters by testosterone supplementation but cannot procreate due to lack of gonadal tissue.

ACQUIRED TESTICULAR DEFECTS:

Viral orchitis may be caused by mumps virus, echovirus, lymphocytic choriomeningitis virus, and group B arboviruses. Orchitis occurs in as many as one-fourth of adult men with mumps; the orchitis is unilateral in about two-thirds and bilateral in the remainder. Orchitis usually develops a few days after the onset of parotitis but may precede it. The testis may return to its normal size and function or may undergo atrophy. Semen analysis returns to normal for three-fourths of men with unilateral involvement but normal for only one-third of men with bilateral orchitis. Trauma, including testicular torsion, can also cause secondary atrophy of the testes. The exposed position of the testes in the scrotum renders them susceptible to both thermal and physical trauma, particularly in men with hazardous occupation.

Radiation and chemotherapy:

The testes are sensitive to radiation damage. Doses >200 mGy are associated with increased FSH and LH levels and damage to the spermatogonia. After 800 mGy, oligospermia or azoospermia develops, and higher doses may obliterate the germinal epithelium. Most boys given direct

testicular radiation therapy for acute lymphoblastic leukemia have permanently low testosterone levels.

Drugs interfere with testicular function by several mechanisms, including inhibition of testosterone synthesis (e.g. ketoconazole), blockade of androgen action (eg.spironolactone), increased estrogen (eg.marijuana), or direct inhibition of spermatogenesis (e.g.chemotherapy).Combination chemotherapy for acute leukemia, Hodgkin's disease, and testicular and other cancers impair Leydig cell function and cause infertility. Cyclophosphamide and combination regions containing procarbazine are particularly toxic to germ cells. Newer regimens like ABVD (Adriamycin, bleomycin, vinblastine, dacarbazine) are less toxic to germ cells.

Alcohol when consumed in excess for prolonged periods, decreases testosterone, independent of liver disease or malnutrition. Elevated estradiol and decreased testosterone levels may occur in men taking digitalis. Testicular failure also occurs as a part of polyglandular autoimmune insufficiency.

Systemic disease can cause primary testis dysfunction in addition to suppressing gonadotropin production. In cirrhosis, a combined testicular and pituitary abnormality leads to decreased testosterone production independent of toxic effects of ethanol. Impaired hepatic extraction of adrenal

androstenedione leads to extraglandular conversion to estrone and estradiol, which partially suppresses LH. Testicular atrophy and gynecomastia is present in one half of men with cirrhosis.

In **chronic renal failure**, androgen synthesis and sperm production decrease despite elevated gonadotropins. About one fourth of men with chronic renal failure have hyperprolactinemia. Sperm density can decrease temporarily after acute febrile illness in absence of a change in testosterone production. Infertility in men with celiac disease is associated with a hormonal pattern typical of androgen resistance, namely elevated testosterone and LH levels.

Neurological diseases associated with altered testicular function include myotonic dystrophy, spinobulbar muscular atrophy and paraplegia. In myotonic dystrophy, small testes may be associated with impairment of both spermatogenesis and Leydig cell function. Spinobulbar muscular atrophy (also known as Kennedy disease) is X-linked and is caused by an expansion of the glutamine repeat sequences in the amino-terminal region of the AR

(androgen receptor). These patients may show evidence of partial androgen insensitivity in adolescence or adulthood. Spinal cord lesions that

cause paraplegia can lead to a temporary decrease in testosterone levels and may cause persistent defects in spermatogenesis.

TREATMENT

Testosterone replacement improves libido and overall sexual activity; increases energy, lean muscle mass and bone density and gives the patient a better sense of well-being.

Injectable forms of testosterone, testosterone enanthate or cypionate are commonly used. Within 24 hours of administration of 200 mg testosterone levels will rise to supraphysiologic levels and then decline slowly over 2 weeks. Testosterone levels should be about 350-600 ng /dl after 1 week of administration.

Two long acting esters, testosterone buciclate and testosterone undeconate, when injected intramuscularly, can maintain circulating testosterone concentrations in the male range for 7-12 weeks.

Transdermal patches of testosterone are also available. 5mg patch a day is able to achieve targeted testosterone levels. 4-6 hours after application testosterone levels should be in mid normal range of 500-700ng/dl.

Testosterone gels like Androgel and Testim, are available in 2.5 and 5gram unit doses that nominally deliver 25 and 50 mg of testosterone to the application site. Gels have found to maintain free and total testosterone in the mid-normal range.

A buccal adhesive testosterone tablet, which adheres to the buccal mucosa and releases testosterone as it is slowly dissolved, has been approved. After twice daily application of 30mg tablets, serum testosterone levels are maintained within the normal male range in a majority of treated hypogonadal men.

After oral administration testosterone is well absorbed but quickly degrades during the first pass through the liver. 17 alpha-alkylated derivatives of testosterone are relatively resistant to hepatic degradation and can be administered orally; however, because of the potential for hepatotoxicity, including cholestatic jaundice, peliosis, and hepatoma, these formulations should not be used for testosterone replacement.

HYPERGONADOTROPIC HYPOGONADISM IN FEMALES

PRIMARY OVARIAN FAILURE

The most common example of hypergonadotropic hypogonadism (i.e. with elevated FSH and LH) and low estradiol is found in Turner syndrome. Between 25% and 40% delayed puberty in girls is of ovarian origin, with Turner syndrome constituting a majority of such patients. Any patient with short stature with webbed neck, cubitus valgus, widely spaced nipples with near normal intelligence with primary infertility should be evaluated for Turner's syndrome with ultra sonogram of the abdomen and pelvis to look for hypoplastic uterus and streak/absent ovaries and with karyotyping to establish the chromosomal defect of 45XO. Patients with variants of Turner's syndrome with mosaic pattern of chromosomal abnormality 45XO/46XX can have near normal uterus and ovaries and they can have normal menstrual cycles and reproductive function.

Gonadal dysgenesis fits the same pattern of high FSH and LH and low estradiol (E2) levels. Gonadal dysgenesis is caused by a mosaic karyotype with an abnormal X chromosome or with a normal karyotype (46, XX) and streak ovaries.

Individuals with Perrault syndrome have gonadal dysgenesis, a normal karyotype, and neuro-sensory deafness. Swyer syndrome is illustrated by a phenotypically immature female with a 46 XY karyotype without testis-determining factor on the Y chromosome. Another rare cause of hypergonadotropic hypogonadism is gonadotropin-resistant ovary syndrome, which is characterized by FSH-resistant ovaries.

Acquired causes of hypergonadotropic hypogonadism can result from high-dose alkylating chemotherapy and radiation treatments to the pelvis. Elevated ESR and anti-ovarian antibody levels may suggest autoimmune oophoritis, but such tests are rarely needed. Autoimmune oophoritis is an exclusionary diagnosis.

HYPOGONADOTROPIC HYPOGONADISM IN FEMALES

Hypogonadotropic hypogonadism occurs when FSH and LH levels are low. Hypogonadotropic hypogonadism may present prior to or after the completion of puberty. The most common causes of hypogonadotropic hypogonadism include chronic illness, starvation, excessive exercise, anorexia nervosa, depression, stress, and marijuana use. Hypogonadotropic hypogonadism involves slowed GnRH release caused by multi-factorial components of decreased body fat and increased beta endorphins.

Chronic illness can affect pubertal development adversely by interfering with metabolism through mal-absorption and poor nutrition (e.g. Crohn disease, diabetes mellitus, hypothyroidism and hyperthyroidism, cystic fibrosis, anorexia nervosa, excessive exercise).

Tumors in the CNS can compress the portal vessels and impede the flow of GnRH from the hypothalamus to the pituitary gland. Pituitary adenomas, craniopharyngiomas, and meningiomas are examples of slow-growing nonmetastatic tumors that are uncommon causes of hypogonadotropic hypogonadism. Anterior pituitary prolactinomas releasing prolactin hormone are the most common pituitary tumors to cause hypogonadotropic hypogonadism.

Other acquired disorders can disrupt pituitary function by destructive means, such as ischemia, infiltration, and obstruction. Head trauma, cranial aneurysms, and infiltrative processes (e.g., sarcoidosis, syphilis, and tuberculomas) are examples of conditions that can disrupt pituitary function.

Abnormal development of the hypothalamus can result in hypogonadotropic hypogonadism. Kallmann syndrome manifests with anosmia, pubertal delay, and a normal response to exogenous gonadotropins. Kallmann syndrome occurs during embryonic development when GnRH secreting neurons fail to migration from the olfactory area to the hypothalamus. The gene KAL1 codes for the protein associated with normal

migration. Other syndromes associated with hypothalamic dysfunction include Prader-Willi syndrome and Laurence-Moon-Biedl syndrome.

TREATMENT

In Turner's syndrome, Conjugated estrogen supplementation, followed by progesterone administration to prevent uterine cancer helps these girls achieve secondary sexual characters.

Turner's syndrome is a condition where recombinant Growth Hormone can be used to increase the height of these girls, other than in Growth Hormone deficiency. [(29)]

In girls with idiopathic hypogonadotropic hypogonadism recombinant FSH and recombinant HCG administration is highly useful for ovulation induction and restoring fertility.

Pulsatile GnRH therapy is highly effective for restoring ovulation in patients with hypothalamic amenorrhea.

In patients with prolactinomas, either bromocriptine administration or transphenoidal hypophysectomy restores pituitary function.

DEGREES OF CONSANGUINITY

Genetically the degree of consanguinity of siblings is the same as that between a parent and child, and both are termed consanguineous in the first degree. An aunt or uncle shares with a niece or nephew about half the chance of common inheritance of a pair of siblings; thus, aunts and uncles may be termed consanguineous kin of the second degree. Following this logic, first cousins who have one-eighth of their genes in common are referred to as consanguineous kin of the third degree. First half cousins who have one-sixteenth of their genes in common are referred to as consanguineous kin of the fourth degree.

MATERIALS AND METHODS

SETTING

The study was conducted on the out patients attending the Institute of Internal Medicine and Department of Medical Endocrinology, Madras Medical College and Government General Hospital, Chennai.

COLLABORATION DEPARTMENTS

Institute of Internal Medicine.

Department of Medical Endocrinology.

ETHICAL COMMITTEE APPROVAL

Institute Ethical Committee approved the study

STUDY DESIGN

Single Center

Non- randomized cross sectional study

STUDY PERIOD

Study was conducted from January 2008 to September 2008 over a period of 9 months

SAMPLE SIZE

In the study period of 9 months, after applying inclusion and exclusion criteria, 50 patients were included.

SELECTION OF STUDY SUBJECTS

INCLUSION CRITERIA:

1. Age- above 12 years.
2. Sex- both genders
3. Patients with underdeveloped secondary sexual characters.
4. Patients with delayed puberty.
5. Patients with primary amenorrhea in girls.

EXCLUSION CRITERIA:

1. Patients with chronic systemic illness
2. Individuals who abuse drugs or alcohol.
3. Patients who have undergone cancer chemotherapy or radiotherapy.

CONSENT

All participants gave written informed consent.

METHODOLOGY.

Detailed history of the patients using a proforma was taken and anthropometric measurements like height, weight and arm span were noted. A thorough general and systemic examination was done to rule out any systemic illness. Secondary sexual characters were assessed using Tanner Staging.

Estimation of hormonal levels was done for all patients in the study. Follicle stimulating hormone, luteinizing hormone, thyroid hormone, cortisol, growth hormone levels, prolactin, testosterone and estradiol levels were assessed.

Radiological assessment including X-ray Cone View Sella, X-ray left forearm and X-ray left wrist was done to asses the bone age and epiphyseal fusion. MRI Brain (Sella) was taken in selected patients to rule out structural causes of pituitary dysfunction.

Karyotyping was also done in certain patients to establish their genotype. Finally, after finding out the etiology of hypogonadism they were started on appropriate treatment.

NORMAL VALUES FOR HORMONES

FOLLICLE STIMULATING HORMONE

Technology used: Fully automated bidirectionally interfaced Chemiluminescent Immuno Assay.

Females

Normally Menstruating; (mIU/ml)

Follicular phase: 2.5-10.2

Midcycle peak: 3.4-33.4

Luteal phase: 0.5-16.9

Pregnant: <0.3

Post menopausal: 23.0-116.3

Males

13-70 years: 1.4-18.1(mIU/ml)

LUTENIZING HORMONE – LH (mIU/ml)

Females- normally menstruating:

Follicular phase: 1.9-12.5

Midcycle peak: 8.7-76.3

Luteal phase: 0.5-16.9

Pregnant: 0.1-6.0

Post menopausal: 15.9-54.0

Children: 0.1-6.0

Males:

20-70 years: 1.5-9.3

>70 years: 3.1-34.6

Free testosterone:

Adult males: 8.9-42.50 pg/ml (pico-gram per ml)

Adult females: 0.02-3.09 pg/ml

KIT used- Biosource, Belgium. Technology used- Radio immune assay.

Total testosterone: in ng/dl (nanograms per dl)

Technology used: fully automated bidirectionally interfaced

Chemiluminescent Immuno Assay.

Age	males	females
1-10 years	2-30	1-20
9.8-14.5 years	5-70	5-30
10.7-15.4years	15-280	10-30
11.8-16.2 years	105-545	15-40
12.8-20 years	280-1100	15-70
20-50 years	241-827	-
Ovulating	-	14-76

ESTRADIOL/ESTROGEN (E2)

UNITS: pg/ml (pico-gram per ml)

Technology used: CLIA- Chemiluminescent Immuno Assay.

Adult female:

Ovulatory cycle (by day in cycle relative to LH peak)

Follicular phase (-12 to -4 days) : 18.90-246.7

Mid cycle (-3 to +2 days) : 35.5-570.8

Luteal phase (+4 to 12 days) : 22.4-256.0

Untreated menopausal : <44.5

Adult males : 11.60-41.20

THYROID FUNCTION TESTS:

FREE T4 (THYROXINE) : 0.70-1.80 ng/dl (nanograms/dl)

Technology used: competitive chemiLuminescent Immuno Assay

Total T4 : 4.5-12.0 microgram/dl

Technology used: competitive chemiLuminescent Immuno Assay

Total T3 : 60-200 ng/dl

Technology used: competitive chemiLuminescent Immuno Assay

TSH : 0.3 -5.5 microIU/ml

Technology used: ultra sensitive sandwich Chemiluminescent Immuno Assay

CORTISOL (mcg/dl) microgram per dl

AT 8 AM: 5- 25

AT 4 PM: 2.5-12.5

Post dexamethasone: below basal level

Post A.C.T.H: Three to five times the basal level

GROWTH HORMONE

ADULTS

BASAL: 0.06-5.0 ng/ml (nanograms per ml)

Post Clonidine stimulation: > 10 ng/ml

Technology used: Chemi Luminescent Immuno Assay

PROLACTIN (ng/ml) nanograms per ml

Males: 2.1-17.7

Females:

Normally menstruating-2.8-29.2

Pregnant: 9.7-208.5

Post menopausal: 1.8-20.3

Technology used: Chemi Luminescent Immuno Assay.

STATISTICAL ANALYSIS

SPSS 13 and Excel were used for statistical analysis

LIMITATIONS

Small number of study subjects especially females

All investigations are not done for every patient.

CONFLICT OF INTEREST

None

RESULTS AND OBSERVATIONS

STUDY POPULATION CHARACTERISTICS

Among the 50 patients included in our study 44 patients were males accounting for 88% of the total. The remaining 12% of patients were females.

According to age, patients who present below 18 years of age were 39 (78%) and above 18 years were 11(22%).

TABLE 1: STUDY POPULATION CHARACTERISTICS

AGE	TOTAL NO OF PATIENTS	%	MALES	FEMALES
<18 years (12-18yrs)	39	78	35	4
>18 years	11	22	6	5

TABLE 2: SEX DISTRIBUTION OF STUDY POPULATION

SEX	HYPOGONADOTROPIC HYPOGONADISM	HYPERGONADOTROPIC HYPOGONADISM
MALES	39	5
FEMALES	2	4

In our study, males were predominant with 44 in number, with females only 6 in number. Among males, 39 had hypogonadotropic hypogonadism and 5 had hypergonadotropic hypogonadism.

In females, 2 of them had hypogonadotropic hypogonadism and 4 of them had hypergonadotropic hypogonadism.

TABLE 3: ETIOLOGY WISE DISTRIBUTION OF HYPOGONADOTROPIC HYPOGONADISM

HYPOGONADOTROPIC HYPOGONADISM	NO: OF

	PATIENTS
IDIOPATHIC	33
KALLMANN SYNDROME	1
VANISHING TESTIS SYNDROME	1
HYPOPITUITARISM	4
GIGANTISM AND HYPOGONADISM	1
CRANIOPHARYNGIOMA	1
TOTAL	41

In our study, a total of 41 patients had hypogonadotropic hypogonadism. Most common etiology was idiopathic hypogonadotropic hypogonadism which is a diagnosis of exclusion.

We found out a patient with bilateral anorchia or vanishing testis syndrome, one patient had kallmann syndrome, four of them had hypopituitarism and interestingly one patient had features of gigantism and hypogonadism.

TABLE 4: ETIOLOGY WISE DISTRIBUTION OF HYPERGONADOTROPIC HYPOGONADISM

HYPERGONADOTROPIC HYPOGONADISM	NO: OF PATIENTS
KLINEFELTER SYNDROME	**5**
TURNER'S SYNDROME	**4**
TOTAL	**9**

In our study, we had 9 patients with hypergonadotropic hypogonadism. Among them 5 had Klinefelter syndrome and 4 had Turner's syndrome.

TABLE 5: CORRELATION BETWEEN DEGREE OF CONSANGUINITY AND PREVALANCE OF HYPOGONADISM

DEGREE OF CONSANGUINITY	NO: OF PATIENTS
NON-CONSANGUINOUS	30
SECOND DEGREE	12
THIRD DEGREE	7
FOURTH DEGREE	1

P value <0.001(highly significant)

In our study, we had a significant negative correlation between consanguinity and occurrence of hypogonadism in children.

TABLE 6: CORRELATION BETWEEN BIRTH ORDER AND HYPOGONADISM

CORRELATION BETWEEN BIRTH ORDER AND HYPOGONADISM

FIRST	21
SECOND	16
THIRD	7
FOURTH	5
FIFTH	1

P value <0.001(highly significant)

In our study, we had a significant positive correlation between birth order and the incidence of hypogonadism.

TABLE 7: COMPARISON BETWEEN STUDY VARIABLES IN MALES

STUDY VARIABLES IN MALES	HYPOGONADISM						
	HYPOG			HYPERG			
	COUNT	MEAN	SD	COUNT	MEAN	SD	P VALUE
ARM SPAN	39	158.62	16.43	5	178.6	6.54	**0.01**
HEIGHT	39	154.51	13.1	5	168.8	3.96	**0.02**
WEIGHT	39	51.8	14.98	5	65.4	10.7	**0.05**
AS-HT	39	4.1	9.93	5	9.8	7.6	0.22
US/LS	39	0.89	0.07	5	0.9	0.04	0.70
FSH	39	1.61	1.28	5	31.6	23.8	**0.001**
LH	25	0.78	0.95	5	16	10.2	**0.001**
TOTAL TESTOSTERONE	39	24.98	24.62	5	61.0	70.1	0.22

P Value 0 to 0.1- significant

P Value 0.011 to 0.05-highly significant

TABLE No. 8 CORRELATION CO-EFFICIENT OF HORMONES AND OTHER VARIABLES - [MALES]

VARIABLES	FSH	LH	TESTO STERONE	ESTRADIOL	ARM SPAN	WEIGHT
FSH	1.00 44 P =.	0.90 30 P=.000	0.21 44 P=0.158	0.98 8 P=0.000	0.23 44 P=0.126	0.34 44 P=0.023
LH	0.90 30 P=0.00	1.00 30 P=.	0.48 30 P=0.006	0.97 6 P=0.11	0.29 30 P=011	0.39 30 P=0.033
TESTOSTERONE	0.21 44 P=0.158	0.48 30 P=0.006	1.00 44 P=.	0.72 8 P=0.041	0.16 44 P=0.28	0.04 44 P=0.769
ESTRADIOL	0.98 8	0.97 6	0.72 8	1.00 8	0.5264 8	0.74 8

	P=0.000	P=0.001	P=0.041	P=.	P=0.180	P=0.035
ARM SPAN	0.23 44 P=0.126	0.29 30 P=0.110	0.16 44 P=0.283	0.52 8 P=0.180	1.00 44 P=.	0.35 44 P=0.019
WEIGHT	0.34 44 P=0.023	0.39 30 P=0.33	0.045 44 P=0.769	0.74 8 P=0.035	0.35 44 P=0.019	1.00 44 P=0.002
HEIGHT	0.29 44 P=0.050	0.34 30 P=0.058	0.11 44 P=0.442	0.57 8 P=0.135	0.81 44 P=0.000	0.45 44 P=0.002

‘.’ IS DENOTED IN CASES WHERE CO-EFFICIENT COULD NOT BE COMPUTED

In males, among the variables studied Arm span, height and weight and FSH and LH varied significantly between hypogonadotropic and hypergonadotropic hypogonadism.

In Males, using correlation coefficients, significant correlation was found between FSH, LH, estradiol and weight.

LH had positive correlation with total testosterone, estradiol and weight.

Total testosterone correlated significantly with LH and estradiol.

Estradiol had positive correlation with FSH, LH and Total Testosterone.

Arm span had significant correlation with weight

Height had significant correlation with FSH, LH, Armspan and weight.

TABLE 9: COMPARISON BETWEEN STUDY VARIABLES IN FEMALES

STUDY VARIABLES IN FEMALES	HYPOGONADISM						P VALUE
	HYPOG			HYPERG			
	COUNT	MEAN	SD	COUNT	MEAN	SD	
ARM SPAN	2	129	4.24	4	143.75	17.0	0.317
HEIGHT	2	126	0.00	4	138.50	16.9	0.38
WEIGHT	2	22.50	3.54	4	35.25	3.69	0.16
AS-HT	2	3.00	4.24	4	5.25	2.22	0.41
US/LS	2	0.90	0.00	4	0.94	0.04	0.32
FSH	2	2.11	0.19	4	95.29	65.75	0.13
ESTRA-DIOL	2	4.15	4.74	4	13.25	1.32	0.16

P Value 0 to 0.1- significant

P Value 0.011 to 0.05-highly significant

TABLE No.10 CORRELATION CO-EFFICIENT OF HORMONES AND OTHER VARIABLES

[FEMALES]

VARIABLES	FSH	LH	ESTRADIOL	ARM SPAN	WEIGHT
FSH	1.00 6 P=.	0.99 3 P=0.021	0.71 6 P=0.109	0.01 6 P=0.446	0.47 6 P=0.338
LH	0.99 3 P=.021	1.00 3 P=.	0.76 3 P=0.446	0.97 3 P=0.145	0.95 3 P=0.187
ESTRADIOL	0.71 6 P=.109	0.76 3 P=0.446	1.00 6 P=.	0.50 6 P=0.310	0.86 6 P=115
ARM SPAN	-0.01 6 P=.984	0.97 3 P=0.145	0.50 6 P=0.310	1.00 6 P=.	0.70 6 P=.143

	0.47	0.95	0.86	0.70	1.00
WEIGHT	6	3	6	6	6
	P=0.338	P=0.187	P=0.27	P=0.115	P=.
	-0.08	0.99	0.38	0.98	0.6731
HEIGHT	6	3	6	6	6
	P=0.872	P=0.032	P=0.446	P=0.000	P=0.143

'.' is denoted in cases where co-efficient could not be computed

In females, significant positive correlation existed between LH and FSH,

Weight and Estradiol, Height and LH, and Height and Arm span.

FIGURE 1:

SEX WISE DISTRIBUTION OF STUDY POPULATION

FIGURE: 2 AETIOLOGY WISE DISTRIBUTION OF

HYPOGONADOTROPIC HYPOGONADISM

FIGURE: 3 AETIOLOGY WISE DISTRIBUTION HYPERGONADOTROPIC HYPOGONADISM

FIGURE 4: PREVELANCE OF GYNECOMASTIA IN HYPOGONADISM MALES

FIGURE 5: CORRELATION BETWEEN CONSANGUINITY IN PARENTS AND HYPOGONADISM

FIGURE 6: CORRELATION BETWEEN BIRTH ORDER AND HYPOGONADISM

DISCUSSION

Individuals who present with hypogonadism can be classified either into hypogonadotropic or hypergonadotropic based on the pituitary hormones and the gonadal hormones.

Most of the individuals in this study presented to us on just entering into adolescence in the age group of 12-15 years, majority below 18 years.

Although most of the individuals with IHH present in adolescence, few of them present in adult age group. In this study we had 5 patients presenting above the age of 18 years with IHH. Similar observation was found by Nachtigall et al. [36]

In this study, most of them who presented with hypergonadotropic hypogonadism, presented above 18 years (5 out of 9).

In this study we had a major proportion of males who presented with hypogonadism than females which may be due cultural practices prevailing in rural areas.

Among hypogonodotropic hypogonadism, in our study, we had Idiopathic hypogonadotropic hypogonadism (IHH) as the most common cause and most of them were males. This correlated well with the study earlier done

by Seminara et al 1998 who showed a male-to-female ratio of nearly 4:1 [Seminara et al 1998] [31]. But in this study we had a very high ratio of 15.5:1 due to small number of females.

The probability of a man being infertile increased as mother's age at birth increased (regression coefficient ± standard error 0.212 ± 0.059; $P < 0.001$), but decreased as birth order increased (regression coefficient ± standard error –0.596 ± 0.230; $P = 0.010$). [37]

As quoted above in the study done by Juan J. Tarín et al., [37] our study also showed that as the birth order increased the probability of having hypogonadism decreases. In other words, the probability of a man being infertile would be greater if he comes from a small family than if he comes from a large family.

In this study, Arm span, height and weight were significantly higher in hypergonadotropic males than hypogonadotropic males. Similar observations were found in a recent study done by Lise Aksglaede, Niels E. Skakkebaek [50] in which they found accelerated growth in early childhood in boys with 47XXY and 47 XYY karyotype. The abnormal stature of these patients may be a result of abnormal gene expression due to the underlying chromosome aberration resulting in excessive expression of growth-related genes.

Using correlation coefficients, significant correlation was found between various study variables.

Total testosterone correlated significantly with LH in males. Similar observation was found in a study done by PC Sizonenko and L Paunier, [49] in which they found major rise of Testosterone, was preceded by the rise of plasma LH and was accompanied by the rise of plasma FSH.

Height had a significant correlation with arm span in both males and females in our study, which correlates well with the similar observation found in the study done by Olabinri B.M, Olawoye T et.al.[51] In their African based study, they found that height showed a high positive correlation with body's armspan in males ($r = 0.916$; $P= 0.001$), and also, a high positive significant correlation exists between height and armspan in female children in Ogbomoso, Nigeria . This finding is in agreement with previous study of Torres et al (2003) who found a high significant correlation between standing height and armspan in children.

SUMMARY

- Hypogonadism is an important problem with which many boys and girls present to the Endocrine out patient department. They experience significant emotional problems due to their reduced secondary sexual characters and delayed puberty. Hence appropriate evaluation and reasonable treatment is of paramount importance in resuming fertility among them. This study was conducted to evaluate such patients and to treat them effectively.

- Most of the individuals presented below the age group of 18 years. Very few presented above 18 years. Many of them above 18 years were found to have hypergonadotropic hypogonadism. Idiopathic hypogonadotropic hypogonadism was the most common cause among below 18 years.

- Among the individuals who presented most of them were males, only a few were females. In males, Idiopathic hypogonadotropic hypogonadism is the commonest cause, whereas in females many of them had Turner's syndrome.

- In our study, we had few patients with interesting causes of hypogonadism like kallmann syndrome, vanishing testis syndrome, craniopharyngioma and with deficiency of other pituitary hormones (hypopituitarism).

- Birth order was found to significantly influence the risk of hypogonadism. As the birth order increased the risk reduced significantly.

- Among the anthropometric variables studied, Arm span, height and weight in males are found to be significantly higher in patients with hypergonadotropic hypogonadism (Klinefelter syndrome), than patients with hypogonadotropic hypogonadism.

- A significant correlation existed between various study variables especially total testosterone and LH in males, and height and arm span in both males and females.

- This study shows the commonest cause of hypogonadism is Idiopathic Hypogonodotropic Hypogonadism and since it is now a treatable condition, early and correct diagnosis is of paramount importance to the individual, family and society at large.

CONCLUSIONS:

1. Most common age group of presentation of hypogonadism patients is below 18 years of age.

2. Hypogonadism is found to be more common in Males than in females.
3. In males, the most common cause is Idiopathic hypogonadotropic hypogonadism.
4. A significant association is present between Birth Order and the incidence of hypogonadism. Most of the patients are first born.
5. Arm span, height and weight varied significantly between Males of hypogonadotropic hypogonadism and hypergonadotropic hypogonadism.
6. A significant correlation existed between total testosterone and LH in males, whereas arm span and height correlated well in both males and females.
7. This study shows the commonest cause of hypogonadism is Idiopathic Hypogonodotropic Hypogonadism and since it is now a treatable condition, early and correct diagnosis is of paramount importance to the individual, family and society at large.

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ABBREVATIONS AND ACRONYMS

FSH	Follicle Stimulating Hormone
LH	Luteinizing hormone
DHT	Di-Hydro-Testosterone
GnRH	Gonadotropin Releasing Hormone
hCG	Human Chorionic Gonadotropin
rhLH	Recombinant Human Luteinizing hormone
GPR54	G Protein-coupled Receptor
ACTH	Adreno-cortico-tropic Hormone
FGFR1	Fibroblast Growth Factor Receptor-1
PROP 1	Prophet of Pit 1
PROK2	Prokineticin 2
AIS	Androgen Insensitivity Syndrome
LHR	luteinizing Hormone Receptor
FSHR	Follicle Stimulating Hormone Receptor

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PROFORMA

PROFORMA FOR HYPOGONADISM

NAME: **AGE:** **SEX:**

ENDOCRINE OP NO:

HISTORY:

H/O of growth abnormality: present or absent

H/O of reduced or delayed development of secondary sexual characters: present or absent

H/O abnormal breast enlargement in males: present or absent

H/O of chronic systemic illness like-

H/O recurrent respiratory infection since birth or childhood-present or absent

H/O heart disease since birth or childhood- present or absent

H/O persistent diarrhea since childhood-present or absent

H/O delayed milestones: present or absent

H/O reduced intelligence: present or absent

H/O neurological illness since birth or childhood: present or absent

H/O abnormality in sense of smell: present or absent

H/O abnormality of vision: present or absent

Family history:

Pedigree chart:

Menstrual history: attained menarche- yes or no

Cycles- regular or not

CLINICAL EXAMINATION:

Height:

Weight:

Arm span:

Head to pubic symphysis (upper segment):

Pubic symphysis to foot (lower segment):

BUILD: OBESE OR THIN

GENERAL EXAMINATION:

ANEMIA CLUBBING CYANOSIS ICTERUS

PEDAL EDEMA LYMPHADENOPATHY

PR: BP:

SYSTEMIC EXAMINATION:

CARDIOVASCULAR:

RESPIRATORY:

ABDOMEN:

NERVOUS SYSTEM:

SMELL:

VISION:

MUSCULOSKELETAL SYSTEM:

SECONDARY SEXUAL CHARACTERS:

BREASTAND NIPPLES:

SCROTUM:

TESTIS: RIGHT:

LEFT:

PENIS:

EXTERNAL GENETALIA - IN FEMALES:

PUBIC HAIR:

AXILLARY HAIR:

INVESTIGATIONS:

FOLLICLE STIMULATING HARMONE:

LEUTINISING HARMONE:

ESTRADIOL:

FREE TESTOSTERONE:

TOTAL TESTOSTERONE:

TOTAL T4:

FREE T4:

THYROID STIMULATING HARMONE:

SERUM CORTISOL: 8 AM:

GROWTH HARMONE:

BASAL:

POST CLONIDINE:

PROLACTIN:

ULTRASOUND ABDOMEN AND PELVIS:

OVARIES: RIGHT:

LEFT:

UTERUS:

TESTIS: RIGHT:

LEFT:

X RAY CONE VIEW SELLA:

X RAY LEFT HANDS:

MRI SELLA:

KARYOTYPING:

DIAGNOSIS:

TREATMENT: